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Review Article

Systemic Chemotherapy is a Promising Treatment Option for Patients with Colonic Stents: A Review

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Abstract

Approximately 10% of patients with colorectal cancer (CRC) develop malignant large bowel obstruction (MLBO) at diagnosis. Furthermore, for 35% of patients with MLBO, curative primary tumor resection is unfeasible because of locally advanced disease and comorbidities. The practice of placing a self-expandable metallic stent (SEMS) has dramatically increased as an effective palliative treatment. Recent advances in systemic chemotherapy for metastatic CRC have significantly contributed to prolonging patients' prognosis and expanding the indications. However, the safety and efficacy of systemic chemotherapy in patients with SEMS have not been established. This review outlines the current status of this relatively new therapeutic strategy and future perspectives. Some reports on this topic have demonstrated that 1) systemic chemotherapy and the addition of molecular targeted agents contribute to prolonged survival in patients with SEMS; 2) delayed SEMS-related complications are a major concern, and this requires strict patient monitoring; however, primary tumor control by chemotherapy might result in decreased complications, especially regarding re-obstruction; and 3) using bevacizumab could be a risk factor for SEMS-related perforation, which may be lethal. Although this relatively new approach for unresectable stage IV obstructive CRC requires a well-planned clinical trial, this therapy could be promising for patients who are unideal candidates for emergency surgery and require immediate systemic chemotherapy.

Keywords

obstructive colorectal cancer, malignant large bowel obstruction, self-expandable metallic stent, chemotherapy, bevacizumab

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Introduction

Colorectal cancer (CRC), with an estimated worldwide mortality of 880,000 in 2018, is the leading cause of cancer-related death[1]. In Japan, CRC was the most commonly diagnosed malignancy and the second leading cause of cancer-related death in 2015[2]. Approximately 10% of patients with CRC develop malignant large bowel obstruction (MLBO) at diagnosis[3,4]. Among patients requiring emergency surgery for colorectal diseases, 85% have MLBO[3,4]. Furthermore, 35% of patients with MLBO are unsuitable for curative primary tumor resection because of locally advanced disease and comorbidities[5].

Previously, invasive surgical approaches, including stoma creation, were the only option for managing MLBO, even in high-risk patients. The frequency of self-expandable metallic

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stent (SEMS) placement has dramatically increased as an effective treatment choice for palliation after its introduction in Japan. A recent meta-analysis reported significant benefits of palliative SEMS placement compared with emergency surgery in terms of morbidity, mortality, and equivalent prognosis[6]. Recent advances in systemic chemotherapy for metastatic CRC (mCRC) have significantly contributed to prolonging the prognosis and expanding the indications in the so-called "vulnerable patients." Most patients with MLBO from mCRC who were candidates for SEMS placement were also outside the indications for systemic chemotherapy in the early period (i.e., purely palliative). However, SEMS placement is now closely associated with systemic chemotherapy, with the expanded indications. Although several reports evaluating the safety and efficacy of systemic chemotherapy in patients who underwent SEMS placement have emerged, the clinical usefulness of this approach is undetermined owing to sparse evidence. In this review article, we describe the current status of systemic chemotherapy for patients with SEMS and its future perspectives.

Optimal Procedures for SEMS Placement

The only indication for SEMS placement in CRC is the presence of both obstructive symptoms and radiological findings suspicious for MLBO. MLBO can occur before the first diagnosis and during treatment with palliative and systemic chemotherapy. A previous systematic review reported that the technical and clinical success rates were 96.2% (range: 66.2%-100%) and 92% (range: 46%-100%), respectively[7]. Notably, results from the pooled analysis of two Japanese multicenter prospective trials of SEMS placement as a bridge to surgery (BTS) were promising, and the study reported technical and clinical success rates of 98.1% and 93.8%, respectively[8,9]. Safe SEMS placement requires expertise and compliance with strict contraindications. The general contraindications for SEMS placement are perforation, penetration, shock state, prophylactic placement, massive invasion to other organs, lower rectal mass within 5 cm of the anal verge, and excessively long or complicated strictures. Obtaining endoscopic biopsies before or during SEMS placement is recommended to confirm malignancy and perform genetic testing for future molecular targeted therapy; however, biopsies are often unfeasible in the emergency setting. Several studies have evaluated the learning curve of successful SEMS placement and have shown that 20 procedures are required to increase technical success and decrease the number of stents per procedure[10,11]. Small et al.[12] reported a higher acute perforation rate in procedures performed by endoscopists inexperienced in pancreaticobiliary endoscopy. A post-hoc analysis of a multicenter study in Japan identified factors related to the technical difficulty in SEMS placement using a cut-off procedure time of 45 min. The authors showed that complete obstruction requiring emergency intestinal decompression, right-sided colon, stricture length over 5 cm, peritoneal carcinomatosis, and multiple SEMS placement were associated with technical difficulty[13]. Detailed information regarding safe SEMS placement is provided in the mini-guidelines established by the Colonic Stent Safe Procedure Research Group (http://colonstent.com).

Pros and Cons of Primary Tumor Resection in Stage IV CRC

The primary goal of treatment for unresectable stage IV CRC is not to achieve a cure but to prolong survival and maintain patients' quality of life (QOL); hence, the main treatment is systemic chemotherapy. Historically, many surgeons have advocated primary tumor resection, mainly to avoid potential primary tumor-related complications, such as bleeding, perforation, or obstruction, and because surgery allows precise tumor staging (e.g., peritoneal metastasis)[14]. Several basic studies have suggested that in the presence of the primary tumor, the liver parenchyma adjacent to metastases provided fertile angiogenic tissue for metastatic tumor growth and may explain the association of primary tumor resection with improved survival[15]. The benefits of primary tumor resection have also been discussed; however, this clinical question has not reached a consensus. Patients with obvious symptoms related to the primary tumor, such as bleeding and obstruction, undergo primary tumor resection. The 2019 Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines[16] state that if symptoms exist as a result of the primary tumor that is difficult to control using other therapies, and resection is not significantly invasive, primary tumor resection and early systemic chemotherapy are recommended. However, patients with unresectable stage IV CRC requiring emergency admission owing to symptoms caused by the primary tumor account for only up to 4% of patients[17]. The oncological advantage of primary tumor resection without symptoms is undetermined. The Japanese guidelines state that the efficacy of resecting an asymptomatic primary tumor has not been established[16]. Recent advances in systemic chemotherapy for mCRC have dramatically prolonged patients' survival and are associated with preferable oncological responses not only at the metastatic site but also in the primary tumor. These developments may have contributed to the paradigm shift from primary tumor resection first to introducing systemic chemotherapy first in daily clinical practice. The annual rate of palliative primary tumor resection has decreased from 74.5% in 1998 to 57.4% in 2010 in the United States[18]. Most studies have demonstrated that primary tumor resection improved oncological outcomes more than in patients without resection; however, these studies were retro-

spective, which involves considerable selection bias caused by choosing patients able to tolerate primary tumor resection[19-21]. In Japan, two large retrospective studies by Shida et al.[22] (n = 770) and Ishihara et al.[23] (n = 1982) using propensity score matching to minimize selection bias demonstrated that primary tumor resection was associated with better overall survival (OS) than no resection (hazard ratio (HR) 0.58, 95% confidence interval (CI) 0.48-0.70, $p < 0.01$; HR 0.41, 95% CI 0.33-0.53, $p < 0.0001$, respectively). However, the study period for patient enrollment for these studies occurred in an earlier era of systemic chemotherapy. Subsequently, Shida et al.[24] identified patients who received systemic chemotherapy consisting of at least one molecular targeted agent, such as bevacizumab, cetuximab, or panitumumab, (n = 208) and used propensity score matching to compare patients with and without primary tumor resection. This more recent study, conducted in the current era of chemotherapy, showed that primary tumor resection was only marginally influential and did not significantly improve OS compared with no primary tumor resection (HR 0.76, 95% CI 0.51-1.15, $p = 0.197$). To clarify the oncological benefit of primary tumor resection in patients with asymptomatic stage IV CRC, several randomized controlled trials (RCTs) have been conducted. Among these, the results of the JCOG1007 trial (iPACS study) (n = 160) were presented at the ASCO-GI 2020[25]. The trial was terminated early based on its futility and demonstrated that primary tumor resection followed by chemotherapy had no superiority regarding OS compared with chemotherapy without primary tumor resection (HR 1.10, 95% CI 0.76-1.59, $p = 0.69$).

When considering resecting a symptomatic primary tumor, surgical risks should be considered. Although the JSCCR guidelines[16] recommend primary tumor resection if the surgery is not significantly invasive for the patient, estimating whether the surgery will be overly invasive is practically difficult. Patients with unresectable stage IV obstructive CRC have poor nutritional status, are immunosuppressed, and suffer from chronic inflammation, which can cause increased postoperative morbidity and mortality[26,27]. A study by Stelzer et al.[28] reported a surprisingly high mortality of 11.7% in patients with unresectable stage IV obstructive CRC who underwent primary tumor resection. The study demonstrated that patients requiring emergency surgery to address primary tumor symptoms had significantly higher mortality than patients undergoing elective surgery (27.8% vs. 7.3%, respectively). A review by de Mestier et al.[29] reported high morbidity and mortality (13%-48% and 2%-11.7%, respectively) after asymptomatic primary tumor resection. Notably, the JCOG1007 trial reported a mortality of 4% and morbidity of 38%, which are considerably higher than those of curative nonmetastatic CRC surgeries[30]. Since initial primary tumor resection can lead to significant delays in introducing effective systemic chemotherapy, and that postoperative complications and surgical stress induce exaggerated inflammatory host responses and decrease tumor immunity, which can result in rapid tumor progression ("surgical oncotaxis")[31-33], primary tumor resection should be performed within strict indications.

Indications for Systemic Chemotherapy in Patients with SEMS

Although unresectable stage IV patients with an obstructive primary tumor can achieve maximal benefits from SEMS placement by avoiding high-risk emergency surgery and permanent stoma creation, which is associated with stoma-related complications and poor health-related QOL[34], the efficacy and safety of systemic chemotherapy after SEMS placement have not been established. Accordingly, primary tumor resection and/or stoma creation should be performed in patients who are candidates for systemic chemotherapy. However, patients with 1) high surgical risk, 2) abundant tumor burden or rapid progression requiring immediate chemotherapy introduction, and 3) declining stoma creation could be candidates for chemotherapy after SEMS placement. Initial SEMS placement permits earlier initiation of chemotherapy, which is superior to delayed chemotherapy administration in terms of QOL and OS[35]. Additionally, the benefits of sequential SEMS placement for subsequent obstructions after prior systemic chemotherapy are assumed. Approximately 20% of patients with prior systemic chemotherapy develop primary tumor obstruction[20,36]. A high mortality rate (3.7%-12.5%) and serious morbidity (7.4%-11.8%) have been reported with palliative surgery for these patients[37-39] suggesting decreased immunity and poor general condition owing to chemotherapy continuation and disease progression. In these patients, the benefits of minimally invasive SEMS placement over surgery would be enhanced.

Previous Reports of Systemic Chemotherapy in Patients with SEMS

Although studies investigating the efficacy of systemic chemotherapy in patients with SEMS are limited to small sample sizes, several studies have demonstrated significantly better survival with systemic chemotherapy in patients with SEMS compared with best supportive care (BSC)[40,41]. However, systemic chemotherapy may increase the risk of SEMS-related complications, such as migration resulting from tumor response, re-obstruction due to in- and outgrowth of the tumor, and perforation, which could be potentially critical[42-44]. Findings in published reports (including patients with and without chemotherapy) have shown procedure- and SEMS-related complications in 5%-23% of patients, with an average rate of SEMS-related perforation in

5% of patients[12,45-47]. Hence, the decision to proceed with SEMS placement must consider the risks of long-term SEMS-related complications weighed against the lower short-term mortality and an earlier start to chemotherapy. Moreover, prolonged survival derived from systemic chemotherapy in patients with SEMS might result in more patients being exposed to the risk of delayed SEMS-related complications[48,49].

Previous representative studies investigating the efficacy and safety of systemic chemotherapy in patients with SEMS are summarized in Table 1[41,50-53]. A multicenter retrospective study by Ceze et al.[50] reported that the response rate and disease control rate in patients who underwent first-line chemotherapy without molecular targeted drugs (n = 38) were 38% and 62%, respectively, and the median progression-free survival (PFS) and OS were 5 months and 18 months, respectively. These oncological outcomes were similar to previous clinical trials using similar regimens (i.e., oxaliplatin- or irinotecan-based regimens without molecular targeted drugs), and the toxicity was generally acceptable at 32% grade 3-4 toxicity among all patients. Although the relatively high perforation rate of 8%, which occurred after 2-15 months of placement, was not negligible, the authors concluded that chemotherapy in patients with SEMS appeared to be a valid option.

Fuccio et al.[51] reported a detailed analysis of 91 patients who underwent palliative SEMS placement, 82 of whom received chemotherapy. The distribution of wild-type and mutant *KRAS* was 48.4% and 51.6%, respectively, which was similar previously reported rates for patients without obstruction. SEMS-related complications constituted re-obstruction in 12.1%, perforation in 8.8%, and migration in 2.2% of patients. The clinical success rates of decompression at 12 and 24 months were 70.7% and 42.2%, respectively. Analyzing only patients who died, revealed clinical success in 78% of the patients, which implied that SEMS had sufficient palliative value until their death in patients treated with systemic chemotherapy. No significant differences in clinical success were observed between chemotherapy-treated patients with and without molecular targeted drugs, and between bevacizumab and cetuximab. Chemotherapy did not influence the risk of SEMS-related complications (Odds ratio (OR) 0.56, 95% CI 0.14-2.9, p = 0.446), and no evidence was found that patients treated with chemotherapy and cetuximab were more likely to experience SEMS-related complications than patients treated with chemotherapy alone or with BSC (OR 1.2, 95% CI 0.2-5.9, p = 0.856). In the OS analysis, patients receiving molecular targeted drugs had significantly longer OS than those receiving only chemotherapy (384 days vs. 240 days, respectively) (risk ratio (RR) 0.5, 95% CI 0.3-0.9, p = 0.02). The study concluded that chemotherapy and using molecular targeted drugs did not influence SEMS-related complications.

Pacheco-Barcia et al.[41] reported a retrospective case series of 78 patients who underwent palliative SEMS placement. Patients were divided into three groups: BSC (n = 31), chemotherapy alone (n = 31), and chemotherapy with bevacizumab (n = 16). The study showed that chemotherapy significantly improved OS compared with BSC (27 months vs. 11 months, respectively; $p < 0.01$) and that bevacizumab showed a significant OS benefit compared with chemotherapy alone (43 months vs. 20 months, respectively; p = 0.02). The overall major SEMS-related complication rate (35%) and perforation rate (5%) equaled those in previous studies, and receiving chemotherapy was an independent risk factor for developing SEMS-related complications (OR 1.84, 95% CI 1.29-6.22, p = 0.007), but not for perforations (OR 1.82, 95% CI 0.33-10.07, p = 0.39). However, bevacizumab treatment showed a nonsignificant trend toward increased perforation rates compared with chemotherapy alone (12.5% vs. 8%, respectively; p = 0.47).

Theoretically, prolonged survival with systemic chemotherapy may increase the risk of SEMS-related complications because chemotherapy prolongs the duration of SEMS implantation in vivo. Abbot et al.[54] reviewed 145 patients undergoing palliative SEMS placement and found that 26.7% experienced delayed SEMS-related complications. Systemic chemotherapy in patients with SEMS was a significant risk factor for delayed complications (OR 5.52, 95% CI 1.76-17.3, p = 0.003) and endoscopic re-intervention (OR 4.30, 95% CI 1.31-14.2, p = 0.018) on multivariate analysis. In contrast, some have the opinion that systemic chemotherapy can prevent SEMS-related complications. Di Mitri et al.[40] showed in a retrospective study of 204 patients who underwent SEMS placement that palliative SEMS placement itself was associated with an increased risk of tumor ingrowth (OR 7.7, 95% CI 1.25-59.7, p = 0.005), but chemotherapy significantly decreased the risk of tumor ingrowth (OR 0.26, 95% CI 0.08-0.83, p = 0.016). Yoon et al.[44] also demonstrated that chemotherapy was a significant negative risk factor for long-term SEMS-related clinical failure (OR 0.52, 95% CI 0.31-0.88, p = 0.015) in a retrospective cohort study of 412 patients with SEMS. These positive effects of chemotherapy against SEMS-related complications, especially for re-obstruction by tumor growth, may have been caused by the effects of tumor shrinkage induced by chemotherapy. However, Fernández-Esparrach et al.[55] strongly suggested that palliative treatment for obstructive primary tumors other than with SEMS placement should be considered in incurable patients eligible for chemotherapy and with a long life expectancy, based on the high rate of long-term SEMS-related clinical failure (51%, 17/33) and subsequent mortality (15%, 8/33).

The previously reported survival of chemotherapy-treated patients after SEMS placement (Table 1) appears to be inferior to that obtained in the current era of aggressive cyto-

Table 1. Previous Representative Studies of Systemic Chemotherapy during SEMS Placement.

Author	Country	Year	Institution	Study Design	Study period	Sample size (%)	Group	Age (range)	Gender (male: %)	Tumor location (left: %)	Interval from SEMS to chemo (days: range)	Regimen	Patency (days: med) (range)	Overall (%)	Migration (%)	Perforation (%)	Reobstruction (%)	PFS (med)	OS (med)
Karoui [52]	France	2007	Single	RS	2000-2005	31	All	72 (35-94)	15 (48.4)	28 (90.3)					5 (16)	2 (6.5)	3 (10)		
						22 (71)	Chemo				14 (3-60)								13.7 m
						9 (29)	BSC												
Lee [53]	Korea	2012	Single	RS	2000-2008	36	Chemo	60.3 (38-84)	22 (61.1)	32 (88.9)	8.1	Overall	115	9 (25.1)	2 (5.6)	1 (2.8)	5 (13.9)		7.6 m
												Oxaliplatin (n = 20)							
												Irinotecan (n = 16)							
Fuccio [51]	Italy	2014	Multi	RS	2007-2011	91	All	64.6 (37-92)	61 (67)	84 (92.3)			90 (4-720)* (*until complication)	21 (23.1)	2 (2.1)	8 (8.8)	11 (12.1)		330 days
						37 (40.7)	Chemo only												240 days
						34 (37.4)	Chemo +BV												384 days
						11 (12.1)	Cehmo +Cet												
						9 (9.9)	BSC												
Ceze [50]	France	2016	Multi	RS	2001-2007	38	Chemo	65 (35-83)	18 (47)	32 (84)	13 (2-62)	Overall	146 (26-1062)	10 (26)	2 (5.3)	3 (7.9)	5 (13)	5m	18m
												FOLFOX (n = 24)							
												FOLFIRI (n = 5)							
												5-FU (n = 8)							
Pacheco-Barcia [41]	Spain	2019	Multi	RS	2012-2017	78	All	76 (med)	29 (37)	73 (94)				27 (35)	2 (2.5)	7 (9)	14 (18)		
						31 (39.5)	BSC		13 (16)	29 (94)				8 (26)	1 (3)	2 (6)	5 (16)		11 m
						31 (39.5)	Chemo alone		13 (34)	29 (94)				13 (42)	1 (3)	3 (9.7)	7 (22.5)		20 m
						16 (21)	Chemo +BV		3 (19)	16 (100)				6 (37.5)	0 (0)	2 (12.5)	2 (12.5)		43 m

RS: retrospective study, chemo: chemotherapy, BSC: best supportive care, SEMS: self-expandable metallic stent, PFS: progression-free survival, OS: overall survival, BV: bevacizumab, Cet: cetuximab, m: month

toxic and molecular targeted therapy, which is approaching a median survival of 30 months[56-58]. Along with SEMS-related complications, long-term survival should be evaluated in future studies with large sample sizes.

Antiangiogenic Agents in Chemotherapy after SEMS Placement

Bevacizumab is a recombinant, humanized monoclonal antibody that binds to and blocks the activity of vascular endothelial growth factor-A, a member of a family of vascular endothelial growth factor receptor-activating ligands. Gastrointestinal perforation is a well-documented side effect of bevacizumab and occurs at a rate of 1%-2%[59]. Bevacizumab administration for patients who underwent SEMS placement increases the risk of perforation[12,60]. Retrospective studies reported an approximately threefold higher rate of perforation in patients who underwent SEMS placement and subsequently received bevacizumab than in those who were not treated with bevacizumab after SEMS placement[12,60]. Bevacizumab-induced perforation during SEMS placement is caused by the radial force of the SEMS on the colonic cancer tissue, which is weakened by the antiangiogenic effect of the drug[61]. In a meta-analysis by Halsema et al.[62], perforation rates in patients treated with chemotherapy with bevacizumab, chemotherapy alone, and BSC were 12.5% (95% CI 6.4-22.8), 7.0% (95% CI 4.8-10.0), and 9.0% (95% CI 7.2-11.1), respectively. The study concluded that bevacizumab-based therapy was a risk factor for perforation, whereas chemotherapy alone was not associated with an increased risk of perforation. In contrast, a recent relatively large retrospective study by Park et al.[63] reported that perforation rates in patients with bevacizumab (n = 96) and without bevacizumab (n = 257) were equivalent at 7.3% and 7.0%, respectively (p = 0.93). The study also showed that chemotherapy did not increase the perforation risk after SEMS placement and that chemotherapy significantly decreased the mortality risk (HR 0.46, 95% CI 0.32-0.68, p < 0.001)[63]. Regarding the perforation risk of SEMS placement in patients with previous bevacizumab use, Bong et al.[64] demonstrated that SEMS was a significant risk factor for complications requiring surgery in patients already receiving bevacizumab (HR 5.69, 95% CI 2.37-13.64, p = 0.001). Halsema et al.[62] also stated in their meta-analysis that SEMS placement should be avoided, if possible, in patients with previous bevacizumab use.

While most cases of SEMS-related complications, such as migration and re-obstruction, can be managed by endoscopic re-intervention with removal and re-stenting, respectively, perforation is difficult to manage with conservative treatment and requires emergency surgical management. Considering that perforation in patients after SEMS placement is associated with higher mortality compared with other complications, perforation cannot be treated uniformly as a complication and should be managed with exceptional caution. Lee et al.[65] analyzed 21 perforated cases after SEMS placement and showed that 14 cases (66.7%) required emergency surgeries, and 5 cases (23.8%) died within 30 days.

Guideline Statements for Chemotherapy after SEMS Placement

The 2019 JSCCR guidelines questioned SEMS placement in patients experiencing obstructive CRC for the first time. The guidelines do not recommend systemic chemotherapy because "Stent treatment is not recommended for patients who are indicated for systemic therapy (Recommendation 2/Evidence level B)"[16]. The guidelines state that this recommendation is based on the possibility of chemotherapy causing tumor shrinkage and tissue necrosis, which can lead to perforation and penetration to surrounding organs.

The European Society of Gastrointestinal Endoscopy (ESGE) guidelines for SEMS for obstructive colonic and extracolonic cancer published in 2014[66] stated that "Patients who have undergone palliative stenting can be safely treated with chemotherapy without antiangiogenic agents" and "given the high risk of perforation, it is not recommended to use SEMS as palliative decompression if a patient is being treated or considered for treatment with antiangiogenic therapy" ("strong recommendation, low quality evidence" in both statements). Notably, this statement conflicts with the Japanese guidelines, which do not recommend SEMS placement, regardless of chemotherapy with or without antiangiogenic agents. The updated version of the 2020 ESGE guidelines[67] essentially followed the previous version but modified the recommendation regarding the association between SEMS and antiangiogenic agent use. The updated guidelines suggest that antiangiogenic therapy can be considered in patients following colonic stenting and do not suggest colonic stenting while patients are receiving antiangiogenic therapy ("weak recommendation, low quality evidence" in both statements)[67]. The World Society of Emergency Surgery (WSES) guidelines on colon and rectal cancer emergencies, which was updated in 2017,[68] state that "alternative treatments to SEMS should be considered in patients eligible to receive a bevacizumab-based therapy" and "Involvement of the oncologist in the decision is strongly recommended" (level of evidence 3 and grade of recommendation B) (Table 2).

Although no data are currently available, the JSCCR and ESGE guidelines[16,66] advise against the use of other agents that inhibit angiogenesis as well as bevacizumab, such as regorafenib, aflibercept, and ramucirumab, because of the speculated high risk of perforation.

Table 2. Guideline Statements for Chemotherapy during SEMS Placement.

Guideline	Source of pulblication	Recommendation and comments	Recommendation Grade/Evidence Level
JSCCR guidelines 2019 for the treatment of colorectal cancer	The Japanese Society for Cancer of the Colon and Rectum（JSCCR）	（Recomendation） • Stent treatment is not recommended for patients who are indicated for systemic therapy （Comments） • Indication should be judged carefully due to the perforation risk by tumor shrinkage and necrosis. • Refrain from bevacizumab use, which can increase the perforation risk. • Other antiangiogenic agents（regorafenib, ramucirumab, aflibercept） are supposed to have similar perforation risk.	2/B
Self-expandable metal stents for colonic and extracolonic cancer: ESGE Guideline - Update 2020	The European Society of Gastrointestinal Endoscopy（ESGE）	（Recomendation） • ESGE recommends chemotherapy as a safe treatment in patients who have undergone palliative colonic stenting. • ESGE suggests antiangiogenic therapy（e.g., bevacizumab）can be considered in patients following colonic stenting. • ESGE does not suggest colonic stenting while patients are receiving antiangiogenic therapy, such as bevacizumab.	Strong/low quality Weak/low quality Weak/low quality
2017 WSES guidelines on colon and rectal cacner emergencies	The World Society of Emergency Surgery（WSES）	（Recomendation） • Alternative treatments to SEMS should be considered in patients eligible for a bevacizumab-based therapy, and involvement of the oncologist in the decision is strongly recommended.	B/3

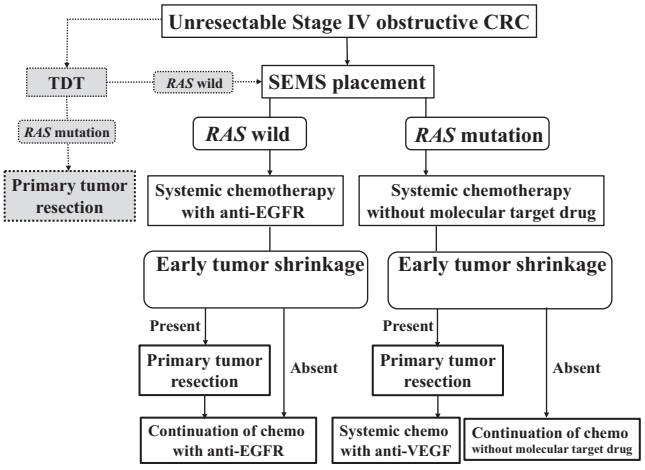

Figure 1. Therapeutic strategy for systemic chemotherapy after SEMS placement.
CRC, colorectal cancer; TDT, transanal decompression tube; SEMS, self-expandable metallic stent.

Our Therapeutic Strategy for Systemic Chemotherapy after SEMS Placement and Future Perspectives

For treating non-curable patients with unresectable stage IV obstructive CRC, it is important to facilitate the quick and safe introduction of systemic chemotherapy in a minimally invasive manner that does not worsen treatment outcomes and that maintains patients' QOL. Among the choices for intestinal decompression, SEMS placement is a promising option that satisfies these goals. However, SEMS placement followed by systemic chemotherapy involves considerable disadvantages, namely, a concern for delayed SEMS-related complications, which could be critical, and the unavailability of bevacizumab (and other antiangiogenic agents). Notably, molecular targeted drugs are not an option for patients with the *RAS* mutation. However, a previous pivotal study evaluating the additional effect of bevacizumab to oxaliplatin-based first-line chemotherapy improved both PFS and OS only for 1.4 months, and the statistically significant difference was observed only in PFS, but not in OS[69]. Additionally, the disadvantage of bevacizumab unavailability might be limited because most patients with obstructive cancers who are candidates for SEMS placement have left-sided CRC, which is associated with less survival benefit with bevacizumab administration than right-sided CRC[70]. Taken together, the considerable above-mentioned benefits of SEMS placement followed by immediate chemotherapy without bevacizumab might outweigh the benefits of bevacizumab availability after invasive surgical intestinal decompression, including stoma creation.

Figure 1 shows our treatment strategy for patients with unresectable stage IV obstructive CRC after SEMS placement. Systemic chemotherapy with anti-epidermal growth

factor receptor (EGFR) antibody and chemotherapy without molecular targeted drugs is introduced as soon as possible after SEMS placement in patients with wild-type *RAS* and *RAS* mutation, respectively. Early tumor shrinkage (ETS) 6-8 weeks after chemotherapy introduction, which is a reliable surrogate marker for better survival[71], is evaluated, and primary tumor resection is planned for patients with ETS. Primary tumor resection in patients with ETS at this time point prevents delayed SEMS-related complications and is associated with longer survival, with the additional effect of bevacizumab administration in patients with the *RAS* mutation. In contrast, patients without ETS are likely to have shorter survival, implying that the benefit of primary tumor resection (i.e., prevention of delayed SEMS-related complications) is relatively limited. Therefore, the continuation of chemotherapy (and a shift to subsequent treatment lines) without primary tumor resection is recommended, with an emphasis on maintaining patients' QOL.

Patients requiring emergency intestinal decompression at the initial visit have a disadvantage in that the physician cannot refer to the patient's *RAS* status before SEMS placement. In patients who are not candidates for emergency surgery, including colostomy, and who require more intensive chemotherapy, temporal intestinal decompression using a transanal decompression tube could be considered until *RAS* status confirmation. SEMS placement followed by chemotherapy with anti-EGFR antibody in patients with wild-type *RAS* and elective primary tumor resection followed by chemotherapy with bevacizumab in patients with the *RAS* mutation might also be effective options.

In Japan, liquid biopsy assessing *RAS* status was covered by the public health insurance system in August 2020. Considering that obtaining biopsy specimens for patients who require emergency SEMS placement is technically difficult, liquid biopsy could be a useful tool for the optimization of anti-EGFR antibody administration and monitoring drug resistance[72].

Conclusions

This review outlined the current status of systemic chemotherapy in patients with SEMS with unresectable stage IV obstructive CRC. Owing to the limited survival benefit and considerable surgical risks, patients with unresectable stage IV obstructive CRC might not be recommended to undergo primary tumor resection. Under such circumstances, it is speculated that the physician will encounter the opportunity to consider systemic chemotherapy after SEMS placement more frequently; however, the related evidence is extremely limited, and conclusions are undetermined. Safe and effective systemic chemotherapy for patients with SEMS is based on compliance with well-considered indications, sufficient informed consent, experienced endoscopists, and strict monitoring for related complications. Although this relatively new approach for unresectable stage IV obstructive CRC requires a well-planned clinical trial, this could be a promising therapeutic option for patients who are unideal candidates for emergency surgery and who require immediate introduction of systemic chemotherapy.

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Conflicts of Interest

There are no conflicts of interest.

Disclaimer

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